IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPEAL BRIEF

Applicant:	Boger, Dale
Serial No.:	10/001,611
Filed:	October 30, 2001
Title:	SYNTHESIS OF CC-1065/ DUOCARMYCIN ANALOGS
Examiner:	L. Stockton
Group Art Unit:	1626
Group:	1620
Technology Center:	1600
Confirmation No.:	1470
Our Ref.:	TSRI 626.1 D1

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Real Party in Interest

The present application has been assigned by all inventors to the Scripps Research Institute, which is the real party in interest.

Related Appeals and Interferences

There are no related appeals or interferences.

Status of Claims

Claims 1, 19, 20, 22-27 and 32 are pending.

Claims 1 and 22-27 were withdrawn from consideration (improperly) by the Examiner.

Claim 32 is rejected.

Claims 2-18 are withdrawn by Applicant.

Claims 21 and 28-31 are cancelled.

Claims 19 and 20 were withdrawn from consideration (improperly) by the Examiner, but are also cancelled herein, without prejudice, by Applicant's request. The impropriety of the Examiner's withdrawal of claims 19 and 20 is rendered mute in view of Applicant's cancellation of these claims.

Status of Amendments

All amendments prior to the final rejection of 12/29/2005 have been entered.

Cancellation of claims 19 and 20 have not yet been entered.

Summary of Invention

Claim 1 is directed to a process for cyclizing a dihydroindole C-ring to form a CC-1065/duocarmycin analog. The process employs two steps. In the first step, an ortho-halo-2-aminonaphthalene is allylated with 1,3-dichloropropene to form a vinyl chloride. In the second step, the vinyl chloride of the first step is cyclized to form the dihydroindole C-ring of the CC-1065 /duocarmycin analog. Support for claim 1 is found in the specification at page 2, lines 22-29; page 4, lines 17-18; page 5, line 26 through page 6, line 6; page 6, lines 7-16; page 7, line 22 through page 8, line 10; and Figure 5.

Claim 22 is a process according to claim 1 wherein the allylation is catalyzed by the addition of a catalytic amount of tetra-*n*-butylammonium iodide. Support for claim 22 is found in the specification at page 2, lines 24-26; and page 7, lines 27-31.

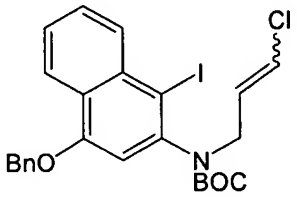
Claim 23 is a process according to claim 1 wherein the cyclization is performed with an addition of tri-*n*-butyltin hydride. Support for claim 23 is found in the specification at page 2, lines 26-29; page 6, lines 2-6; page 8, lines 3-10; and Figure 5.

Claim 24 is a process according to claim 23 wherein the cyclization is catalyzed by the addition of a catalytic amount of AIBN. Support for claim 24 is found in the

specification at page 2, lines 26-29; page 6, lines 2-6; page 8, lines 3-10; and Figure 5.

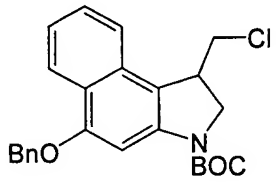
Claim 25 is a process according to claim 24 wherein the cyclization is performed using toluene as the solvent. Support for claim 25 is found in the specification at page 2, lines 26-29; page 4, lines 23-25 (condition "d" of Figure 6); page 6, lines 2-6; page 6, lines 10-14; page 8, lines 3-10; and Figure 5.

Claim 26 is a process according to claim 1 wherein the vinyl chloride is represented by the following structure:

and 

;

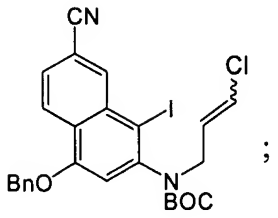
CC-1065/duocarmycin analog is represented by the following structure:



.

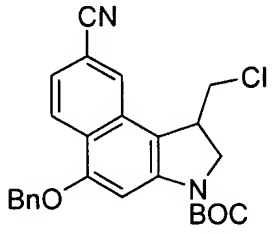
Support for Claim 26 is found in Figures 5 and 6.

Claim 27 is a process according to claim 1 wherein the vinyl chloride is represented by the following structure:



;

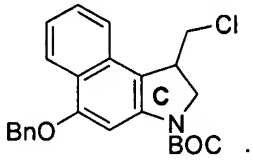
and the CC-1065 /duocarmycin analog is represented by the following structure:



.

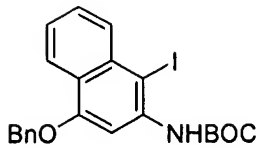
Support for Claim 26 is found in Figure 6.

Claim 32 is a process for synthesizing a dihydroindole C-ring of a CC-1065/duocarmycin analog. In this process, the dihydroindole C-ring of the CC-1065/duocarmycin analog being represented within the following structure:

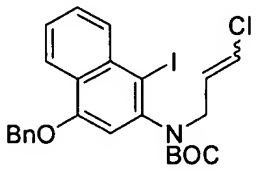


.

The process employs two steps. In the first step, an *ortho*-haloaniline is allylated with 1,3-dichloropropene to form a vinyl chloride. The *ortho*-haloaniline being represented by the following structure:



The vinyl chloride is represented by the following structure:



In the second step, the vinyl chloride is cyclized to form the dihydroindole C-ring of the CC-1065 / duocarmycin analog. Support for Claim 32 is found in the specification at page 2, lines 22-29; page 4, lines 17-18; page 5, line 26 through page 6, line 6; page 6, lines 7-16; page 7, line 22 through page 8, line 10; and Figure 5.

Grounds of Rejection to be reviewed on Appeal

Issue 1:

Were claims 1 and 22-27 improperly withdrawn from examination by the Examiner?

More particularly, are claims 1 and 22-27 drawn to a non-elected invention?

Issue 2:

Does the specification satisfy the written description requirement under 35 USC §112, first paragraph, with respect to claim 32?

Arguments

Issue 1:

Were claims 1 and 22-27 improperly withdrawn by the Examiner? More particularly, are claims 1 and 22-27 drawn to a non-elected invention?

Responsive to a restriction requirement, mail dated 10/01/2002 (paper number 5), Applicant elected the process in Figure 6 for making compound 12(a) of Figure 6. The process for making compound 12(a) of Figure 6 is illustrated in Figure 5. The process has two steps. The second of the two steps is directed to a cyclization which results in the formation of a dihydroindole C-ring.

The Examiner objects that a process for "cyclizing" the dihydroindole C-ring is a different inventive concept as compared to a process for "synthesizing" a dihydroindole C-ring. The Examiner withdrew claims 1 and 22-27 are being drawn to a non-elected invention.

Applicant traverses this objection.

The concept of cyclizing a molecule is a subset of the concept of synthesizing the molecule. That is, all molecular cyclizations are synthetic processes, but not all

synthetic processes are cyclizations.

The 1986 version of the International Dictionary of Medicine and Biology defines the terms "synthesize" and "cyclization" as follows (see evidence Appendix):

> "Synthesize": To **form** (**a** substance or **molecule**) by chemical **reaction**, especially by reaction that builds up the molecule from simpler ones."

> "Cyclization": A **reaction** in which two parts of a **molecule** combine so that a ring of atoms is **formed** within the **molecule**, sometimes with addition of another molecule to complete the ring."

Applicant's replacement of the term "synthesizing" in claims 1 and 22-27 with the term "cyclizing" was a narrowing of these claims. The amendment was made so as to clarify that the claimed process for making the dihydroindole C-ring necessarily includes a cyclization step, i.e., two parts of a **molecule** combine so that a ring of atoms is **formed** within the **molecule**.

The Board is requested to return the instant application to the Examiner with instructions to examine claims 1 and 22-27.

Issue 2:

Does the specification satisfy the written description requirement under 35 USC §112, first paragraph, with respect to claim 32?

The Examiner alleges that there are three deficiencies with respect to the written description requirement, viz.:

a.) lack of support for the "C-ring";

b.) lack of support for the allylation step, except with specific reagents, conditions, etc. ; and

c.) lack of support for the cyclization step, except with specific reagents, conditions, etc.

Applicant traverses all three basis for this rejection.

a.) Lack of support for the "C-ring":

Support for the concept of the "C-ring" in compound **12(a)** is found in the Specification as follows:

"Treatment with Bu_3SnH and a catalytic amount of AIBN (AIBN=2,2'-azobisisobutyronitrile) with heating in benzene or toluene very cleanly effected 5-exo-trig radical cyclization **to form the 3-chloromethyl indoline C-ring** present in each of the analogs **(12a-g)** as illustrated in FIG. 6." (Specification, page 6, lines 2-6)

b.) Lack of support for the allylation step, except with specific reagents, conditions, etc.

Broad support for the concept of the allylation step is found in the Specification as follows:

> "The appropriately functionalized aryl halides **(10a-g)**, which were obtained either through direct electrophilic halogenation (entries 1-5) or directed ortho metallation (entries 6 and 7) and halide quench, were **alkylated** with 1,3 dichloropropene to complete the radical cyclization precursors **(11a-g)** in high yields." (Specification, page 5, line 29 through page 6, line 2)

Figure 5 illustrates that the alkylation of compound **10(a)** to form **11(a)** is an allylation type alkylation. The above references to the specification teaches that the allylation step may be achieved broadly.

c.) Lack of support for the cyclization step, except with specific reagents, conditions, etc.

Broad support for the concept of the cyclization step is found in the Specification as follows:

"More particularly, the invention comprises the 5-exo-trig radical **cyclization** of an aryl halide onto a tethered vinyl chloride forming the dihydroindole C-ring with chlorine installed as a suitable leaving group for subsequent cyclopropane spirocyclization." (Specification, page 5, lines 2-6)

Further support in the specification is found as follows:

"The invention is directed to a two-step transformation directed to the synthesis of 6 CC-1065/duocarmycin analogs using a novel intramolecular aryl radical **cyclization** onto a vinyl chloride to form the dihydroindole C-ring found in 6 CC-1065/duocarmycin analogs." (Specification: page 5, lines 2-6) (Specification, page 1, Technical Field, lines 4-8)

The above references to the specification teach that the cyclization step may be achieved broadly.

Summary:

Claims 19-20 have been cancelled without prejudice. Claims 1 and 22-27 were improperly withdrawn from examination by the Examiner, as being drawn to a non-elected invention. Applicant asserts that claims 1 and 22-27 correspond precisely to the elected invention. The Board is requested to return the application to the Examiner for examination of claims 1 and 22-27. Claim 32 was rejected for lack of support in the specification with respect to written description. Applicant asserts that Claim 32 is fully supported by the written description. The Board is requested to reverse this basis for rejection of claim 32 and to return the application to the Examiner for further examination of claim 32.

Respectfully submitted,

Sept 25, 2006
Date

Donald G. Lewis, Reg. No. 28,636

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Listing of claims on Appeal:

Claim 1: A process for cyclizing a dihydroindole C-ring to form a CC-1065/duocarmycin analog, the process comprising the following steps:

Step A: allylating an *ortho*-halo-2-aminonaphthalene with 1,3-dichloropropene to form a vinyl chloride, then

Step B: cyclizing the vinyl chloride of said step A to form the dihydroindole C-ring of the CC-1065 /duocarmycin analog.

Claim 19: cancelled

Claim 20: cancelled

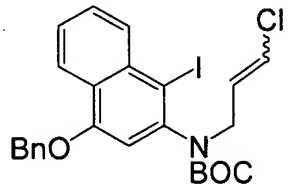
Claim 22: A process according to claim 1 wherein, in said Step A, said allylation is catalyzed by the addition of a catalytic amount of tetra-*n*-butylammonium iodide.

Claim 23: A process according to claim 1 wherein, in said Step B, said cyclization is performed with an addition of tri-*n*-butyltin hydride.

Claim 24: A process according to claim 23 wherein, in said Step B, said cyclization is catalyzed by the addition of a catalytic amount of AIBN.

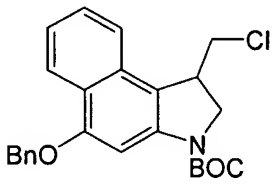
Claim 25: A process according to claim 24 wherein, in said Step B, said cyclization is performed using toluene as the solvent.

Claim 26: A process according to claim 1 wherein, in said Step A, the vinyl chloride is represented by the following structure:



; and

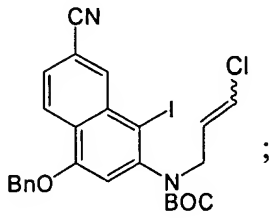
in said Step B, the CC-1065/duocarmycin analog is represented by the following structure:



.

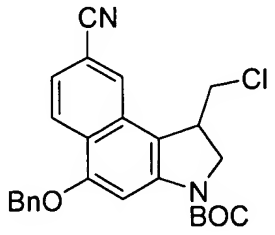
Claim 27: A process according to claim 1 wherein:

in said Step A, the vinyl chloride is represented by the following structure:



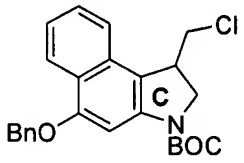
; and

in said Step B, the CC-1065 /duocarmycin analog is represented by the following structure:



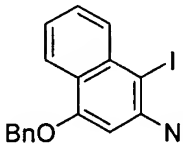
.

Claim 32: A process for synthesizing a dihydroindole C-ring of a CC-1065/duocarmycin analog, the dihydroindole C-ring of the CC-1065/duocarmycin analog being represented within the following structure:



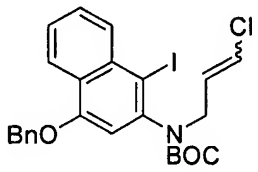
the process comprising the following steps:

Step A: allylating an *ortho*-haloaniline with 1,3-dichloropropene to form a vinyl chloride, the *ortho*-haloaniline being represented by the following structure:



; and

the vinyl chloride being represented by the following structure:



; then

Step B: cyclizing the vinyl chloride of said step A to form the dihydroindole C-ring of the CC-1065 / duocarmycin analog.

INTERNATIONAL DICTIONARY OF MEDICINE AND BIOLOGY

IN THREE VOLUMES

Volume I

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purulent cyclitis A very severe inflammation of the anterior uveal tract that results in an outpouring of leukocytes into the aqueous humor.

serous cyclitis Inflammation of the anterior uveal tract that permits a fine suspension of plasma proteins to enter the aqueous humor.

cyclization [*cycl(e)* + *-iz(e)* + -ATION] A reaction in which two parts of a molecule combine so that a ring of atoms is formed within the molecule, sometimes with addition of another molecule to complete the ring.

cyclizine $C_{18}H_{22}N_2$. 1-Diphenylmethyl-4-methylpiperazine. An antihistaminic agent used as an antiemetic and to prevent motion sickness. It is usually given as the hydrochloride or lactate salt.

cyclo- [Gk *kyklos* a ring, circle, circular body; in pl. *kykloi* the eyeballs] **1** A combining form meaning (1) circular or cyclical; (2) the ciliary body. **2** A combining form indicating that a molecule, often of a hydrocarbon, contains a ring. Also *cycl-*.

cycloamylose A substance composed of glucose residues joined to form a cyclic array of α1,4-linked units. Such substances, with six, seven, or eight residues, show some of the properties of enzymes, binding substrates within their rings and providing an environment that catalyzes certain chemical reactions. Also called *Schardinger dextrin.*

cycloanemization [CYCLO- + *anem(o)-* + -IZE + -ATION] An antiglaucoma operation that reduces the formation of aqueous humor by destroying the part of the circulation to the ciliary body which is derived from the long ciliary arteries.

cycloartenol A C_{30} sterol, with a methylene group joined to C-9 and C-10 to form a cyclopropane ring. It is the first steroid made in the pathway by which squalene is converted into sterols in plants. (Lanosterol plays a similar role in animals.) It is made by isomerization of squalene 2,3-epoxide, which is also the precursor of animal sterols.

cyclobarbital $C_{12}H_{16}N_2O_3$. 5-(1-Cyclohexen-1-yl)-5-ethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione. A barbiturate which is short to intermediate-acting, with sedative and hypnotic activities. It is given orally.

cyclobutanol $CH_2—CH_2—CH_2—CH—OH$ A secondary cyclic alcohol, having a boiling point of 123°C.

cyclocephalia CYCLENCEPHALY.

cyclocephalus CYCLENCEPHALUS.

cyclocephaly CYCLENCEPHALY.

cycloceratitis CYCLOKERATITIS.

cyclochoroiditis [CYCLO- + CHOROIDITIS] Inflammation of the entire uveal tract.

cyclocryotherapy [CYCLO- + CRYOTHERAPY] Freezing of the ciliary body, performed to reduce the secretion of aqueous humor in glaucoma.

cyclodamia [CYCLO- + Gk *dam(an)* to subdue + -IA] A refracting technique in which the spontaneous tendency of a hyperope to accommodate is relaxed by use of convex spheres.

cyclodeviation [CYCLO- + DEVIATION] A torsional fault of eye position, due to rotation upon the anteroposterior axis.

cyclodialysis [CYCLO- + DIALYSIS] The surgical separation ior axis.

cycloelectrolysis [CYCLO- + ELECTROLYSIS] A glaucoma operation in which the rate of formation of aqueous humor is reduced by damaging the ciliary body with an electrical current.

cyclogram [CYCLO- + -GRAM] A recording of the function of the ciliary body.

Cyclogyl A proprietary name for cyclopentolate hydrochloride.

cycloheximide An antibiotic obtained from certain strains of *Streptomyces griseus* that inhibits the peptidyl transfer reaction of protein synthesis in eukaryotic cells but not in prokaryotes or mitochondria.

cycloid [CYCL- + -OID] Recurrent or periodic: used of both the acute, recurring, self-limited mood swings of manic-depressive or bipolar disorders and the less extreme alternations between self-satisfaction and general disaffection that are characteristic of cyclothymic personality.

cycloisomerase Any enzyme that catalyzes the addition to a double bond of another part of the substrate molecule, thus forming a ring. Such enzymes are classified as EC 5.5. An example is the enzyme that interconverts glucose 6-phosphate and inositol phosphate.

cyclokeratitis [CYCLO- + KERATITIS] Inflammation of both the ciliary body and the cornea. Also *cycloceratitis.*

cyclo-ligase Any of a small class of enzymes (EC 6.3.3) that catalyze the formation of a ring within a molecule and the concomitant hydrolysis of a nucleoside triphosphate. An example is phosphoribosylimidazole synthetase, which is responsible for the formation of the imidazole ring during purine synthesis.

cyclomastopathy [CYCLO- + MASTOPATHY] An inflammatory or proliferative response of breast tissue to various stimuli.

cyclomethycaine $C_{22}H_{33}NO_3$. 4-(Cyclohexyloxy)benzoic acid 3-(2-methyl-1-piperidinyl)propyl ester. A local anesthetic usually employed as the hydrochloride or the sulfate. It acts on the skin and mucosa of the rectum and genitourinary tract, but is less effective on the mucous membranes of the mouth, nose, and eye. It is formulated in an aerosol, cream, ointment, jelly, and suppository.

cyclomorphosis A seasonal change in morphology that occurs with certain species of planktonic organisms.

cyclo-oxygenase An enzyme present in most cells that catalyzes the formation of the vasoactive prostaglandins thromboxane and prostaglandin I_2. The acetylation of cyclo-oxygenase by aspirin is the basis for aspirin's antiplatelet-aggregating role. Also called *prostaglandin synthetase.*

cyclopean [Gk *Kyklōpei(os)* pertaining to the Cyclopes + English *-an*, adjectival suffix] Pertaining to or marked by the anomaly of having a single midline eye: said of an embryo or fetus.

cyclopentamine $C_9H_{19}N$. *N*, α-Dimethylcyclopentaneethanamine, a sympathomimetic drug that produces relatively little central excitation and useful systemic pressor activity. It is used primarily for local application as a vasoconstrictor to the nasal mucous membranes or to the eye. It is usually used as the hydrochloride.

cyclopentolate hydrochloride $C_{17}H_{25}NO_3 \cdot HCl$. α-(1-Hy-

rice synovitis Chronic synovitis characterized by the presence of fibrocartilaginous loose bodies resembling grains of rice.
scarlatinal synovitis Synovitis occurring as a complication of scarlet fever.
serous synovitis Synovitis associated with a tense joint effusion consisting of serous fluid.
synovitis sicca Synovitis characterized by relatively little joint effusion. Also called *dry synovitis.*
simple synovitis Synovitis marked by an effusion consisting of slightly turbid fluid.
suppurative synovitis PURULENT SYNOVITIS.
tendinous synovitis TENOSYNOVITIS.
transient synovitis A joint effusion with synovial inflammation that completely subsides without sequelae after a period of days or weeks. Also called *transitory synovitis.*
transitory synovitis TRANSIENT SYNOVITIS.
traumatic synovitis Inflammation of the synovium following injury to a joint.
tuberculous synovitis Synovitis resulting from direct infection with *Mycobacterium tuberculosis.*
vaginal synovitis TENOSYNOVITIS.
vibration synovitis Synovitis caused by the blast effect of a missile passing close to a joint.
villonodular synovitis PIGMENTED VILLONODULAR SYNOVITIS.

synovium An outmoded term for MEMBRANA SYNOVIALIS CAPSULAE ARTICULARIS.

synphalangism SYMPHALANGY.

synpneumonic Occurring during pneumonia.

synprolan PITUITARY SYNERGIST.

synreflexia Associated or simultaneous movements other than the reaction or response expected during the elicitation of a reflex.

synsacrum [SYN- + SACRUM] A bone in birds, which is formed by the fusion of the posterior thoracic, all of the lumbar, all of the sacral, and some caudal vertebrae, and which attaches to the pelvis ventrally.

synsepalous Possessing sepals that are united, at least in part. Also *gamosepalous.*

syntasis [Gk *syntasis* (from *synteinein* to stretch together, strain) a stretching together, straining] A stretching.

syntaxis ARTICULATION.

syntectic [Gk *syntēktik(os)* tending to dissolve, waste away] Characterized by wasting.

syntenic Of or relating to two or more genes that are present on the same chromosome regardless of whether linkage has been demonstrated between the loci.

syntenosis A diarthrodial joint surrounded by tendons, such as the articulations of the digits.

synteny [Gk *syntein(ein)*syn- SYN- + *teinein* to stretch, aim at) to increase, tend toward, aim at + -Y] The state of two or more genetic loci being present on the same chromosome, regardless of linkage.

synteresis PROPHYLAXIS.

synteretic [Gk *syntērētik(os)* watching closely] PROPHYLACTIC.

syntexis [Gk *syntēxis* a wasting away] WASTING.

synthase Any enzyme that catalyzes synthesis of a compound, such as citrate synthase, which catalyzes the synthesis of citrate. The term once excluded enzymes whose reactions involve breakdown of nucleoside triphosphates (i.e. synthetases), but these are now also considered synthases, e.g. glutamine synthase.

synthermal [SYN- + THERMAL] ISOTHERMIC.

synthesis [Gk *synthesis* (from root of *syntithenai* to place or put together, from SYN- + Gk *tithenai* to place, put, set) a putting together, compounding, composition] (*plural* syntheses) The formation of a substance or molecule by chemical reaction, especially by a reaction that builds up the molecule from simpler ones.
de novo synthesis Synthesis from simple starting compounds, rather than by recovery of only partly degraded material.
distributive synthesis A technique of psychobiology that strives to identify the major factors whose union will provide the greatest security to the patient and the most dependable basis for coping with life.
inducible enzyme synthesis The production of an enzyme whose synthesis is increased by an inducer, suchas the substrate of the enzyme or an analogue thereof.
morphologic synthesis 1 HISTOGENESIS. 2 ORGANOGENESIS.
unscheduled DNA synthesis Any synthetic activity of nuclear DNA that occurs at a time in the cell cycle when the chromosomes are not replicating; hence, occurring outside the S phase. It is usually detected by incorporation of radioactive precursors. One reason for this activity is the repair of damage, as that induced by ultraviolet or x-irradiation.

synthesize To form (a substance or molecule) by chemical reaction, especially by a reaction that builds up the molecule from simpler ones.

synthesizer / speech synthesizer An electronic system that produces speech output from character input, used, for example, in reading machines for the blind.

synthetase Any enzyme that catalyzes synthesis of a compound with concomitant breakdown of a nucleoside triphosphate. The term is sometimes incorrectly used for synthases in general. Also called *ligase.*
heme synthetase FERROCHELATASE.

synthetic Produced by synthesis; especially, artificially produced by chemical synthesis rather than obtained from a natural source.

synthetism OSTEOSYNTHESIS.

synthorax [SYN- + THORAX] THORACOPAGUS.

Synthroid A proprietary name for sodium levothyroxine.

Syntocinon A proprietary name for oxytocin.

syntone [back-formation from *syntonic*, from Gk *synton(os)* (from *syn* with + *tonos* tone, tenor) in unison with + -IC] A syntonic person.

syntonic Attuned to the environment; in harmony with one's surroundings.

syntopic Pertaining to syntopy.

syntopie SYNTOPY.

syntopy [SYN- + Gk *top(os)* a place + -Y] The location of an organ in relation to the surrounding organs. Also *syntopie.*

Syntropan A proprietary name for amprotropine phosphate.

syntrophism [SYN- + TROPH- + -ISM] CROSS-FEEDING.

syntrophoblast SYNCYTIOTROPHOBLAST.

syntropic [SYN- + -TROPIC[1]] 1 In anatomy, turning, pointing, or arranged in the same direction: used especially of parts forming a series of segments, such as the ribs on one side or the spines of thoracic vertebrae. 2 Converging and leading in the same direction, as qualities or diseases.

syntropy The state of being syntropic.
inverse syntropy Reduction (possibly to zero) of the likelihood of occurrence of one disease in a patient or group by the presence of another disease in that patient or group. For example, a person with sickle cell anemia is unlikely to contract malaria.

syntype [SYN- + TYPE] Any of several specimens from which